Complete Summary

GUIDELINE TITLE

Bortezomib in multiple myeloma and lymphoma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Reece D, Imrie K, Smith CA, Stevens A, Hematology Disease Site Group. Bortezomib in multiple myeloma and lymphoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr. 36 p. (Evidence-based series; no. 6-18). [33 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Multiple myeloma
- Waldenstrom's macroglobulinemia
- Lymphoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the efficacy of bortezomib alone or in combination in patients with multiple myeloma, Waldenstrom's macroglobulinemia, or lymphoma, as measured by survival, quality of life, disease control (e.g., time-to-progression), response duration, or response rate
- To evaluate the toxicity associated with the use of bortezomib
- To determine which patients are more or less likely to benefit from treatment with bortezomib

TARGET POPULATION

Adult patients with myeloma, Waldenstrom's macroglobulinemia, or lymphoma of any type, stage, histology, or performance status

INTERVENTIONS AND PRACTICES CONSIDERED

1. Bortezomib
2. Oral alkylating agent-based chemotherapy

MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Disease control (e.g., time-to-progression)
- Response duration
- Response rate
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (Ovid) (1966 through October 2004), Medline Daily Update (October 22, 2004), Medline In-Process & Other Non-Indexed Citations (October 22, 2004), HealthStar (1975 through September 2004), CINAHL (1982 through October 2004), EMBASE (Ovid) (1982 through 2004 Week 42), and the Cochrane Library (2004, Issue 4) databases were searched. The search strategy for MEDLINE is shown in Appendix 1 in the original guideline document; searches in other databases were similar. Literature searches were not restricted for publication type or study design.

In addition, conference proceedings of the American Society of Clinical Oncology (1995-2004) and the American Society of Hematology (1996-2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guideline Clearinghouse (http://www.guideline.gov/), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles of study designs of any type (including systematic reviews, meta-analyses, and evidence-based practice guidelines) were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts in the English language of:

1. Studies including adult patients with myeloma, Waldenstrom's macroglobulinemia, or lymphoma (any histologic subtype, stage, performance status, or disease type)
2. Studies evaluating bortezomib as a single agent or in combination with other regimens
3. Comparative trials, in which bortezomib could be compared with any agent, any combination of agents, or placebo
4. Results reporting one or more of the following outcomes: survival, quality of life, disease control (e.g., time-to-progression [TTP]), response duration, response rate, or adverse effects

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types
2. Studies reporting fewer than 20 patients (all disease types combined)

Article Selection

Citations in the initial search of the literature were reviewed by two independent reviewers for inclusion. Citations were not blinded for the selection process. Each citation was scored as "Yes" (inclusion criteria were met, no exclusion criteria were met), "No" (one or more exclusion criteria were met), or "Maybe" (unclear from the citation if article meets any criteria). All discrepancies were resolved by consensus between the two reviewers and, if necessary, scored by a third reviewer. Interobserver kappa coefficients were calculated using GraphPad QuickCalcs © (GraphPad Software, Inc.) (http://graphpad.com/quickcalcs/kappa1.cfm). Any subsequent exclusions of selected articles were documented.

NUMBER OF SOURCE DOCUMENTS

In total, 20 publications of 16 trials in myeloma and lymphoma were identified. For myeloma, one randomized controlled trial (RCT), one randomized phase II trial, four non-randomized phase II trials, and five dose-escalation trials were included. For lymphoma, four non-randomized phase II and one phase I/II trials were included.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data appropriate for pooling or meta-analysis are not expected but will be investigated if the possibility exists. For planned analyses, the primary outcome of interest is progression-free survival, secondary outcomes of interest are response rate and overall survival, and subset analyses will be conducted by histology.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by two member of the PEBC Hematology Disease Site Group (DSG).

This systematic review is a convenient and up-to-date source of the best available evidence on bortezomib in multiple myeloma and lymphoma. The body of evidence in this review is primarily comprised of randomized controlled trial (RCT) data. That evidence forms the basis of a clinical practice guideline developed by the Hematology DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review

Section 2 in the original guideline document reports the results of the systematic review of bortezomib for patients with multiple myeloma and lymphoma. On the basis of that evidence and the interpretation by members of the Disease Site Group (DSG), draft recommendations were developed and circulated to Ontario practitioners for feedback. Section 3 in the original guideline document details the results from the practitioner feedback, changes made to the draft report, and the final recommendations that were submitted to the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP) for review and final approval.

The recommendations were submitted with the systematic review (Section 2 in the original guideline document) to a sample of 161 hematologists, medical oncologists, and radiation oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 15, 2005, and reminder cards and complete repeat mailings sent thereafter.

Report Approval Panel

The final evidence-based series report was reviewed and approved by the Program in Evidence-based Care Report Approval Panel in March 2006. The Panel consists of two members, including an oncologist, with expertise in clinical and

methodology issues. No significant issues were raised by the panel, and the report was approved for distribution.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Based on the results of a large well conducted randomized controlled trial (RCT), which represents the only published randomized study in relapsed myeloma, the Hematology Disease Site Group (DSG) offers the following recommendations:

- For patients with myeloma refractory to or relapsing within one year of the conclusion of initial or subsequent treatment(s) (including autologous stem cell transplantation) who are candidates for further chemotherapy, bortezomib is recommended as the preferred treatment option.
- Bortezomib is also a reasonable option for patients relapsing at least one year after autologous stem cell transplantation. The Disease Site Group is aware that thalidomide, alkylating agents, or repeat transplantation may also be options for these patients. However, evaluation of these other options is beyond the scope of this Practice Guideline.
- For patients with myeloma relapsing at least one year after the conclusion of alkylating agent-based chemotherapy who are candidates for further chemotherapy, further treatment with alkylating agent-based chemotherapy is recommended.
- There is insufficient evidence to support the use of bortezomib outside of clinical trials in patients with non-Hodgkin's lymphoma or Waldenstrom's macroglobulinemia.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized and non-randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized controlled trial (RCT) compared bortezomib with high-dose dexamethasone in patients with relapsed myeloma and reported superior median time to progression (6.2 versus 3.5 months; $p<0.001$) and greater one-year survival (80% versus 66%; $p=0.003$) in the bortezomib arm.
- Two phase II trials, the Stanford University Medical Media and Information Technology (SUMMIT) and Carotid Revascularization Endarterectomy versus Stent Trial (CREST) trials, reported response rates of 33-44% with median

response durations of 9.5-13.7 months. In both studies, the addition of dexamethasone in non-responders increased the response rate by 18-33%.

POTENTIAL HARMS

- One randomized controlled trial (RCT) that compared bortezomib with high-dose dexamethasone in patients with relapsed myeloma, reported that Grade 3 adverse events were more common in the bortezomib arm (61% versus 44%; p=0.01).
- See the original guideline document for a detailed review of the toxicities observed in the trials reviewed.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- There is limited evidence to support the appropriateness of a specific time-to-relapse period as being indicative of treatment-insensitive disease. The one-year threshold provided in the above recommendations is based on the opinion of the Hematology Disease Site Group (DSG).
- For specific details related to the administration of bortezomib therapy, the DSG suggests clinicians refer to the protocols used in the major trials. Some of those details are provided below for informational purposes:
    - Regarding dosage, bortezomib 1.3 mg/m^2 is given as a rapid intravenous bolus over 3-5 seconds on days 1, 4, 8 and 11 of a 21-day cycle; a minimum of 72 hours between doses is required to allow for the recovery of normal proteasome function. Vital signs should be checked before and after each dose. A complete blood count is recommended before each dose, with blood chemistries, including electrolytes and creatinine levels, monitored at minimum on days 1 and 8 of each cycle. The dose of bortezomib should be reduced or held immediately for the development of painful neuropathy, as described in the product monograph; dose modification may also be required for peripheral sensory neuropathy without pain, or other toxicities. Most toxicities are reversible if dose modification guidelines are followed.
    - Responses to treatment are usually apparent by six weeks (two cycles). For patients achieving complete remission (CR) (determined by negative electrophoresis and immunofixation), bortezomib should be given for two additional cycles beyond the date of confirmed complete remission. In patients with progressive disease after two cycles, or stable disease after four cycles, dexamethasone (20 mg by mouth [po] the day of, and the day after each bortezomib dose) added to the bortezomib regimen may produce an objective response. Bortezomib (with or without dexamethasone) should be continued in patients showing benefit from therapy (excluding those in complete remission), unless disease progression or significant toxicity is observed. Therapy should be discontinued in patients who do not respond to bortezomib alone if disease progression is seen within two cycles of the addition dexamethasone.
- The Hematology DSG recognizes that thalidomide is an active agent in treating patients with multiple myeloma who have relapsed after autologous stem cell transplantation or are refractory to alkylating agent-based

chemotherapy. To date, there are no randomized controlled trials reporting evaluations of thalidomide in this role, and, specifically, no trials comparing thalidomide with bortezomib. With these limitations, members of the Hematology DSG regard thalidomide or bortezomib to be alternative therapies to dexamethasone.

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Apr 3

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The working group members for this topic and the Chair of the Hematology Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this evidence-based series. The lead author of this evidence-based series was the principal investigator or the local investigator and received research funding for four trials, including the randomized controlled trial (RCT) reported here. That author was also a consultant for the manufacturer of bortezomib, received honoraria, and was an advisory board participant for a future trial.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Bortezomib in multiple myeloma and lymphoma: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Apr 3. Various p. (Practice guideline; no. 6-18). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 29, 2006. The updated information was verified by the guideline developer on July 7, 2006.

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DISCLAIMER

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Readers with questions regarding guideline content are directed to contact the guideline developer.

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